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REVIEW ARTICLES

Extrapulmonary and Disseminated Infections Due to *Mycobacterium malmoense:* Case Report and Review

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Mycobacterium malmoense **is a potentially pathogenic species that was first described in 1977. During the past decade *M. malmoense* has been recognized with increasing frequency as a pulmonary pathogen. More than 180 cases of *M. malmoense* infection have been reported. Most of these infections affected a previously damaged lung. Other infection sites included the skin, lymph nodes, and bursae. Five cases of disseminated infection have been reported. The antituberculous drugs associated with the most favorable susceptibility patterns are rifampin and ethambutol. Because of the slow growth of *M. malmoense* on conventional, egg-based bacteriologic media, the incubation time should be >6 weeks; special solid and liquid media are recommended. We report a case of disseminated pulmonary and gastrointestinal infection due to *M. malmoense* in a patient with AIDS, who was treated successfully with a combination of rifabutin (ansamycin), clofazimine, and isoniazid. In addition, we review the characteristics of extrapulmonary and disseminated infections due to *M. malmoense.***

Human disease caused by *Mycobacterium malmoense* is rare. More than 180 cases of *M. malmoense* infection have been reported since this potentially pathogenic nontuberculous species of *Mycobacterium* was first described by Schröder and Juhlin in 1977 [1]. Most of these cases consisted of pulmonary disease that, in terms of symptomatology and manifestations, resembled pulmonary infection due to *Mycobacterium tuberculosis.* Nevertheless, two important differences were noted in cases of infection due to *M. malmoense:* (1) a poor correlation between results of in vitro drug susceptibility tests and clinical response to chemotherapy [2–4] and (2) a lack of transmission to healthy contacts (whether such infection can be transmitted to immunocompromised persons has not been decided [5–10]. Therefore, infection-control and contact-tracing procedures need not be applied in response to *M. malmoense* infections. In contrast with extensive reports of pulmonary infections [11–17], case reports of extrapulmonary and disseminated disease due to *M. malmoense* have been sparse.

Parallel to the continuing epidemic of AIDS, an increasing incidence of diseases caused by either *M. tuberculosis* or nontuberculous mycobacteria (NTM) has been observed [9, 18]. In persons with advanced AIDS, *Mycobacterium avium* complex (MAC) is the most frequent cause of mycobacterial infection; in addition, disseminated infection due to MAC is one of the most common opportunistic infections in this patient population [9, 10, 19]. Nevertheless, other species of NTM, including *Mycobacterium kansasii* and *Mycobacterium haemophilum,* have also been shown to cause disseminated disease in patients with AIDS [20, 21]. In 1985 Good reported the first finding of a single isolate of *M. malmoense,* which was recovered in the laboratories of the Centers for Disease Control (CDC; Atlanta) from a pool of mycobacterial isolates from 212 patients with AIDS [22]. In the meantime, the recovery of three clinically significant *M. malmoense* strains from specimens from men infected with the human immunodeficiency virus (HIV) in developing countries was reported [23].

The first cases of pulmonary and disseminated disease due to *M. malmoense* in HIV-infected men were described in 1991 [24]. We report herein another case of disseminated infection with *M. malmoense* in a patient with AIDS and review the characteristics of 21 cases of extrapulmonary and disseminated disease due to *M. malmoense.*

Case Report

In October 1990 a 42-year-old homosexual man complained of having had severe night sweats, fever, productive cough, and severe watery diarrhea for the previous 3 weeks. In 1986 serology for HIV had been found to be positive. In February 1989, HIV infection in CDC stage IVA associated

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with impaired cellular immunity (CD4 lymphocyte count, 40/mm^3) had been diagnosed after weight loss, intermittent diarrhea (results of staining of stool specimens for acid-fast bacilli were negative), and persistent fever with night sweats were reported. At that time, therapy with zidovudine was started. In February 1990 the HIV infection had shown signs of further progression with the development of oral candidiasis (CDC stage IVC2).

When we examined the patient in October 1990, he was thin and almost cachectic. Generalized micropolyadenopathy was noted. Loud, widespread rhonchi, corresponding to a history of heavy smoking and chronic obstructive lung disease, were heard during auscultation. There were no auscultatory signs of pneumonia. No hepatosplenomegaly was found. Results of clinical laboratory tests were not remarkable except for a slightly elevated level of alkaline phosphatase. Routine hematology showed (zidovudine-induced) macrocytic anemia (hemaglobin concentration, 12 g/dL) and a normal leukocyte count with normal differentiation. The sedimentation rate was higher than normal but unchanged in comparison with that noted in previous tests (78 mm/h). The CD4 lymphocyte count had declined to 10/mm^3. A roentgenogram of the chest showed a newly developed acinar infiltrate in the right upper lobe; no abnormalities had been noted on a roentgenogram obtained 7 months before. Neither apical scarring nor mediastinal or hilar lymphadenopathy were evident. Ultrasonography of the abdomen revealed slightly enlarged paraaortal and hepatohilar lymph nodes. Microscopic examination of specimens of sputum (seven times), feces (five times), and bronchoalveolar lavage fluid (one time) yielded acid-fast bacilli. A tuberculin skin test with 2 IU (corresponding to 5 U) of PPD-S produced no reaction. Antituberculous therapy was started with isoniazid (300 mg/d), pyrazinamide (1,800 mg/d), and rifampin (720 mg/d).

After 4 weeks, mycobacterial culture of stool and sputum yielded NTM and the therapeutic regimen was modified; rifabutin (ansamycin, Farmitalia Carlo Erba AG, Zug, Switzerland; 600 mg/d), clofazimine (300 mg/d), ethambutol (1,500 mg/d), and isoniazid (300 mg/d) were administered. At 7 weeks his condition was unchanged, and the severe diarrhea, cough, and fever had not abated. Meanwhile, *M. malmoense* was identified on the basis of testing with standard biochemicals and the fatty-acid profile (obtained with gas-liquid chromatography). The patient was treated with isoniazid (300 mg/d), rifabutin (600 mg/d), and clofazimine (200 mg/d). The administration of ethambutol had to be discontinued because of gastrointestinal side effects). *M. malmoense* was found in five stool specimens and seven sputum samples (all smears were microscopically positive for acid-fast bacilli). Cultures of blood (4 samples) and urine (1 sample) for mycobacteria remained negative. With use of the proportion method and Middlebrook 7H10 agar plates, it was determined that the isolated strain was susceptible to rifampin (MIC, 1.0 mg/L), rifabutin (0.12 mg/L), and clofazimine (1.0 mg/L) and resistant to isoniazid (1.0 mg/L), ethambutol (16 mg/L), streptomycin (2.0 mg/L), amikacin (5.0 mg/L), cycloserine (50 mg/L), ofloxacin (2.0 mg/L), and ciprofloxacin (2.0 mg/L). (The proportion method demonstrates susceptibility when, at a given concentration, the yield of cfu is <1% of that obtained with a drug-free control.)

The patient continued to suffer from coughing, slight hemoptysis, and severe watery diarrhea. Bronchoalveolar lavage revealed severe chronic bronchitis and microscopically numerous acid-fast bacilli (later confirmed as *M. malmoense*), but no other cause of the pulmonary disease was evident. Transbronchial biopsy showed a nonspecific lymphocytic inflammation of the lung tissue, in which no acid-fast bacilli, granulomas, or giant cells were detected. A culture for mycobacteria of a transbronchial biopsy tissue specimen was not performed.

During the following 6 months, diarrhea and coughing gradually dissipated. The infiltrate in the right upper lobe started to decrease in size. The patient's compliance with therapy was confirmed several times by detection of isoniazid metabolites and, initially, by the characteristic red color of rifampin in urine. After 10 months of antituberculous treatment, results of microscopic examination and cultures of sputum and feces were negative, and the patient's condition improved. The diarrhea had disappeared completely, and there was only little coughing; a chest roentgenogram showed scar formation in the right upper lobe but no more evidence of an infiltrate. The patient resumed work on a part-time basis. The clinical symptoms did not recur. Treatment was continued until 15 months after the diagnosis, and all specimens of stool and sputum remained negative for acid-fast bacilli.

Literature Review and Discussion

In reviewing the English-language literature for all previously reported cases of extrapulmonary and disseminated infections with *M. malmoense*, we referred to two sources, *Index Medicus* and *Current Contents*, under the subject headings *nontuberculous mycobacteria* and *M. malmoense*. In addition, we checked the reviewed literature for further references to cases of extrapulmonary and disseminated infections due to *M. malmoense*. The search of the literature from 1967 to September 1992 yielded 15 published reports describing extrapulmonary infection with *M. malmoense*. Adequate descriptions of treatment and clinical course were not always available, especially in regard to cases of cervical lymphadenitis. Overall, 21 cases of extrapulmonary and disseminated infection due to *M. malmoense* were described in 15 reports.

Clinical Manifestations

The characteristics of all 21 cases of extrapulmonary and disseminated infections due to *M. malmoense* are listed in

Table 1. Characteristics of cases of disseminated infection due to *M. malmoense.*

Case no.	Reference	Patient age (y)/ sex	Underlying disease or risk factor	Site of infection and manifestations	Clinical features	Diagnostic findings	Treatment	Outcome and comments
1	[25]	59/F	Atypical chronic granulocytic leukemia treated for 12 mo with busulfan and thioguanine	Disseminated; pulmonary and cutaneous manifestations	Chronic cough, multiple subcutaneous abscesses	Fine nodular opacities on chest radiographs, positive cultures of subcutaneous abscess specimens	Rifampin, isoniazid, ethambutol	Early death
2	[26]	40/M	Hairy-cell leukemia treated with α-interferon 2b	Disseminated (most probable because of poor general condition); enlarged lymph nodes of the upper mediastinum and infiltration of the lung	Protracted fever (temperatures to 40°C)	Widening of the upper mediastinum; mediastinoscopy with lymph node biopsy: granulomatous infiltrates with Langhans' giant cells; microscopy: acid-fast bacilli; culture: positive for *M. malmoense*	Rifampin, doxycycline, ethambutol, cycloserine (16 months), then isoniazid only	Remainined afebrile, gained weight; general condition still improving
3	[27]	48/F	Chronic myeloid leukemia (Philadelphia chromosome positive)	Disseminated, initially, supraclavicular lymph node; 6 mo later, multiple tender indurations, skin nodules on the forearm, back, buttocks, and thighs	Night sweats, anorexia, lethargy, weight loss, fever, (temperatures to 38°C), no lymphadenopathy or splenomegaly	Lymph node biopsy numerous acid-fast bacilli (no culture) Liver biopsy: nonnecrotizing granulomata (no culture) Biopsy of cutaneous lesions: giant and epithelioid cells, no acid-fast bacilli; culture: positive for *M. malmoense*	Rifampin, isoniazid; pyrazinamide subsequently added Streptomycin added (no improvement) Final regimen: cycloserine, ethambutol (dramatic improvement)	Healing of the skin lesions noted in several weeks and liver function normal within 2 months with cycloserine and ethambutol therapy; treatment stopped after 9 mo; no relapse in $5\frac{1}{2}$-y follow-up
4	[24]	56/M	AIDS (CD4 lymphocyte count, 30/ mm^3) Cigarette smoking Alcohol abuse	Disseminated (most probable) Base and midzone of the right lung Gastroinestinal tract	Weight loss, night sweats, anorexia Persistent cough, tachypnea Jaundice, bowel disturbance, peripheral neuropathy, hepatic encephalopathy	Sputum: acid-fast bacilli; culture: positive for *M. malmoense* Stool: acid-fast bacilli, culture: positive for *M. malmoense* Abdominal ultrasonography: dilated gall bladder (no gall stones) ERCP: common bile duct displaced and narrowed	Rifampin, isoniazid, pyrazinamide initially (no improvement); ethambutol subsequently added (after 9 mo sputum cultures became negative, but 4 mo later deterioration was noted)	Hepatorenal failure, then death
5	Present report	42/M	AIDS (CD4 lymphocyte count, 40/ mm^3) Cigarette smoking	Disseminated (most probable) Anterior upper lobe (typical for NTM)	Poor general constitution, intermittent fever, night sweats, weight loss Coughing, hemoptysis	Smears of feces and sputum repeatedly positive; culture: positive for *M. malmoense* Bronchoalveolar lavage: evidence of severe chronic bronchitis, numerous acid-fast bacilli	Rifabutin, clofazimine, isoniazid	After 6 mo, coughing and diarrhea disappeared; after 8 mo, patient resumed work (part time); no relapse

Table 1. (*Continued*)

Case no.	Reference	Patient age (y)/ sex	Underlying disease or risk factor	Site of infection and manifestations	Clinical features	Diagnostic findings	Treatment	Outcome and comments
				Gastrointestinal tract	Diarrhea tenesmus	Transbronchial biopsy: nonspecific, lymphocytic inflammation of lung tissue, no giant cells, no acid-fast bacilli (no culture); no other pathogens		

NOTE. ERCP = endoscopic retrograde cholangiopancreatography.

tables 1, 2, and 3. Three patterns can be distinguished among the clinical manifestations.

Disseminated infections (table 1). Five cases of disseminated infection due to *M. malmoense* have been described (present report included) [24–27]. In all five cases, there was an underlying cause of immunodeficiency: chronic granulocytic leukemia, hairy-cell leukemia, and chronic myelocytic leukemia in one case each and AIDS in two cases. In the two cases in which AIDS was the underlying disease, the peripheral blood CD4 lymphocyte count was $<100/mm^3$. A definitive diagnosis was made after cultures of specimens from a subcutaneous abscess (cases 1 and 3), from mediastinal lymph node biopsy (case 2), and of stool and sputum (cases 4 and 5) were positive for *M. malmoense*. In cases 3, 4, and 5, a final diagnosis of disseminated disease could not be made on the basis of results of cultures of blood, bone marrow, and liver punction specimens; nevertheless, on the basis of the general constitution of the patients, such a diagnosis appears likely. The cases involving AIDS fulfill the criteria for a diagnosis of disseminated disease due to NTM in cases of HIV infection, according to the guidelines of the American Thoracic Society (ATS) [10]. The outcomes of the five cases of disseminated disease included death in two cases (in case 1, antituberculous treatment was given only for a short time, but the patient had a progressive underlying disease; in case 4, hepatorenal failure developed after the patient's condition had improved for after a short time because of antituberculous therapy). In the other three cases, the patients were cured by antituberculous treatment according to the results of in vitro susceptibility tests performed after 16 months (case 2), 9 months (case 3), and 8 months (case 4) of treatment, respectively.

Tenosynovitis (table 2). Another disease pattern is represented by three cases of local *M. malmoense* infection in bursae, one in a hand [28] and two in a forearm [29, 30]. Two of these cases were associated with risk factors. In case 6 (hand abscess), the patient had insulin-dependent diabetes and had received a cortisone injection at the site of the abscess after swelling of the hand was misinterpreted as a ganglion. In case 8 (tenosynovitis of forearm flexors with carpal tunnel syndrome), the patient was an active gardener whose illness probably was the result of reactivation of *M. malmoense* infection that had occurred years previously after traumatic injury of the hand with a rose thorn (for which local steroid treatment was administered). In case 7 (tenosynovitis of forearm flexors with carpal tunnel syndrome), the patient recalled no traumatic incident in which inoculation of *M. malmoense* might have occurred.

Cervical lymphadenitis (table 3). Unilateral cervical lymphadenitis presenting as abscess is the most frequent extrapulmonary infection due to *M. malmoense* [2, 8, 13, 16, 31], although other lymph regions can also be affected (e.g., mediastinal or submandibular lymph nodes) [11, 32]. Constitutional symptoms are generally absent. In contrast with pulmonary disease, which occurs predominantly in adults, all diagnosed cases of lymphadenitis, except one involving a 75-year-old woman with swelling in the submandibular region, have been in children [11].

Historical Aspects

In 1967 Birn et al. published a study of *M. avium* and related NTM in which they described five strains that differed from *M. avium* in terms of lipid pattern, serotype, ethionamide resistance, and temperature range for growth [34]. These strains were susceptible to both cycloserine and ethionamide and were either negative or weakly positive for arylsulphatase. The justification for defining a new species (at that time named "provisional new species two") was the distinctive pattern of its surface lipids observed on chromatography. Four of the five strains were considered to be definitely clinically significant. All were the cause of pulmonary disease in persons who had pneumoconiosis as an underlying disease. In 1969 Schaefer et al. gave further clinical details and reported that two patients with infection due to the mycobacteria died [33]. Ten years later, in 1976, Schröder sent seven strains of mycobacteria from Germany to the *Mycobacterium* Reference Unit in Wales, which identified them as identical to organisms of the "provisional new species two". In 1977 Schröder and Juhlin described the new species in a

Table 2. Characteristics of cases of tenosynovitis due to *M. malmoense.*

Case no.	Reference	Patient age (y)/ sex	Underlying disease or risk factor	Site of infection	Clinical features	Diagnostic findings	Treatment	Outcome and comments
6	[28]	52/M	Insulin-dependent diabetes and cortisone injection because of painful swelling	Left hand	May 1985: swelling of the left hand	Ganglion	Oct 1985: cortisone injection	Not determined
					Feb 1986: tender scar, sinus discharging clear fluid	Serous fluid and xanthochromatic granules	Surgery (sinus excision)	
					May 1986: swelling returned (painful)	Radiography and bone scanning: no evidence of osteomyelitis		
					May 1988: swelling tender, firm, not fluctuating	Pigmented villonodular synovitis; biopsy: epithelioid granulomata (caseating), many acid-fast bacilli; culture: positive for *M. malmoense*	Rifampin, isoniazid, pyrazinamide	
7	[29]	73/M	No specific history of trauma (infection spread hematogenously?)	Vaginae synoviales of forearm flexors	Disturbance of median nerve sensation	Carpal tunnel syndrome	Initially, surgical decompression (not successful, synovitis)	After 12 mo, antituberculous therapy discontinued; patient remained asymptomatic for 2 subsequent years
						Granulomatous tenosynovitis with Langhans' giant cells, no acid-fast bacilli; culture: positive for *M. malmoense*	Surgical intervention, no antituberculous therapy (not successful)	
							Surgical intervention (because of relapse 5 mo after second surgery), this time with antituberculous therapy (rifampin, ethambutol)	
8	[30]	61/F	Asthma; 5 mg prednisolone daily for the last 10 y; corticosteroid injection in the right carpal tunnel because of signs of nerve compression; injury to right thumb from a rose thorn years previously	Synovium of the forearm flexor tendons	Loss of sensation in the median nerve	Carpal tunnel syndrome	Surgical decompression and isoniazid, rifampin, ethambutol, pyrazinamide (but relapse occurred)	Condition improved, swelling resolved, median nerve sensation regained; wasting of thenar muscles still noted
					Wasting of thenar muscles	Histologic examination: nonspecific, chronic synovitis		
					Fluctuant swelling of the volar forearm	Acid-fast bacilli in initial smear of specimen from second synovectomy; culture: positive for *M. malmoense*	Second extensive tenosynovectomy; antituberculous therapy (?)	

report on taxonomic studies, in which they proposed the name *M. malmoense* because organisms of the new species had been first isolated from patients in the Swedish town of Malmö [1]. Jenkins and Tsukamura reported that from 1954 to 1979 61 isolates of *M. malmoense* had been recovered from 11 patients [2]. A retrospective review of these records showed that *M. malmoense* was first isolated in 1954, at which time it was not yet identified as a separate strain [11]. In addition, it may well be possible that before 1954, in cases in which results of histologic or microscopic examination were positive but cultures were negative for mycobacteria, some of the isolates recovered were *M. malmoense.* In 1979 the first two extrapulmonary infections (cervical lymphadenitis in two patients in England) were described [2].

Microbiology

On the basis of colonial morphology, *M. malmoense* could be misidentified as the *Mycobacterium terrae* complex or MAC. *M. malmoense* is distinguished from *M. shimoidei* by only one feature, acid phosphatase activity, of which the detection is among the few tests that are commonly used to identify mycobacteria. It seems that *M. malmoense* isolates do not grow optimally on Löwenstein-Jensen culture medium slants. Therefore, incubation time for primary isolation should be prolonged to 8–12 weeks [35]. However, growth is enhanced by the use of acidic egg-based media [36, 37], media supplemented with either pyruvate [38] or isoniazid [39], or radiometric broth 12B [40]. Results of this study showed that broth culture with the Bactec system (Johnston Laboratories, Towson, MD) was significantly more sensitive and rapid for the detection of *M. malmoense* in tissue samples than was culture on solid, egg-based medium. *M. malmoense* hydrolizes Tween 80, has no acid phosphatase activity, shows microaerophilic growth [1], and does not grow at 45°C. Because *M. malmoense* is a rare etiologic agent for extrapulmonary mycobacteriosis, we recommend that clinically significant isolates should be identified and that their identification be confirmed at laboratories with experienced personnel. The chromatography techniques used in these laboratories produce results faster than do traditional biochemistry tests.

Epidemiology

Little is known about the epidemiology of *M. malmoense*. The possibility that the higher number of isolates of this new species is the result of greater experience in its identification can be denied today, since a review of the records in the *Mycobacterium* Reference Unit in Wales since 1954 revealed only a few strains for which the mycobacteriological identification was wrong [11]. Thus, improvement in laboratory techniques per se cannot be the cause of this increase. Today there is no doubt of a genuine increase of infections due to *M. malmoense*, including those infecting sites such as the skin and bursae. Nevertheless, on the basis of figures from 1987, Ellis found that *M. malmoense* has a relatively high affinity for the respiratory tract in comparison with other NTM [41]. The ratio of respiratory to nonrespiratory cases of infection due to *M. malmoense* was ~6, whereas for infections due to other pathogens it was as follows: *M. tuberculosis*, 2.7; *M. kansasii*, 18; MAC, 2.4; and *Mycobacterium xenopi*, 25.

The most common extrapulmonary infection due to *M. malmoense* is cervical adenitis, which has been found to occur almost exclusively in children. Katila et al. showed that in 12 cases of bacteriologically verified cervical adenitis in Finland between 1977 and 1986, MAC was identified in nine, *M. malmoense* in two, and *M. tuberculosis* in only one [31]. In addition, they drew the interesting conclusion that neonatal BCG vaccination seems to protect children against nontuberculous mycobacterial infections. This conclusion was based on the fact that the incidence of nontuberculous mycobacterial adenitis became 30 times greater in Sweden than in Finland after neonatal BCG vaccination had been stopped. Whether their theory holds true in regard to protection against infection due to *M. malmoense* has not been established.

Disseminated infections have only been described as occurring in association with an underlying immunodeficiency such as leukemia or AIDS.

Clinical Significance of Isolates

In contrast with other NTM, *M. malmoense* has been isolated only from human sources and from captured wild armadillos (*Dasypus novemcinctus*) in Louisiana [42]—never from an inanimate source. Colonization of the gastrointestinal tract in healthy persons has been reported previously by Portaels et al. [43], but the ramifications of this finding in terms of epidemicity have not been determined. They found *M. malmoense* in the stool of one patient and *Mycobacterium simiae* along with *M. malmoense* in the stool of another. Whether mycobacteria found in the gastrointestinal tract are occasional colonizers or a part of the permanent flora has not been determined.

The presence of characteristic clinical signs and the isolation of *M. malmoense* from a biopsy specimen that demonstrates histopathological signs of granulomas normally are indicative of disease, i.e., in bursae or lymph nodes. However, most specimens are of sputum; thus, although recovery of an isolate may indicate disease, it may also indicate transient contamination of the oropharynx or benign colonization of the lung (i.e., in association with chronic bronchitis), especially if mycobacteria cannot be repeatedly cultured [44–46].

The present case fulfills the criteria recommended by the ATS for diagnosis of pulmonary disease caused by NTM [10], although lung tissue samples did not show any acid-fast bacilli because of sampling error. The transbronchial biopsy specimen was not cultured for acid-fast bacilli. It seems that bronchoalveolar lavage results in a higher diagnostic yield than does transbronchial biopsy; this has already been shown for *M. tuberculosis* [47]. The absence of typical histologic signs of mycobacterial disease such as granulomas or giant cells is relatively common in cases of AIDS [48]. Granuloma formation in HIV-infected patients depends on their state of immune reactivity.

Positive stool cultures are also difficult to interpret because asymptomatic patients with stool cultures positive for

Table 3. Characteristics of cases of lymphadenitis due to *M. malmoense*.

Case no.	Reference	Patient age (y)/sex	Underlying disease or risk factor	Site of infection	Clinical features	Diagnostic findings	Treatment	Outcome
9	[33]	9 mo/M	None	Cervical lymph node	Small scald	Cold abscess; direct smear: acid-fast bacilli; culture: positive for *M. malmoense*	Surgery (radical curettage); riampin, isoniazid (6 mo)	Neck fully healed
...	[8]	Mean, 5.2 y range, 1.8–9.7 y/12 F and 7M	None, except in one case	Cervical nodes (47%); submandibular nodes (32%); preauricular nodes (21%); unilateral, 84%	Swelling (mean duration, 6.6 w) in 63%, minimal tenderness and fluctuation (suggestive of cold abscess); glands: 1.5–7 cm; no systemic upset; chest radiography clear for 88%	Acid-fast bacilli in 61%; cultures positive at 7.9 w; sensitivity results obtained in 11.5 w (no specific data given)	Incision and drainage (61%)	
10	[8]	(Child)			Prominent right hilus	No caseating granulomas	Partial excision; incision and drainage	Uncomplicated (no sinus)
11	[8]	(Child)				Caseating granulomas	Needle aspiration	Sinus for 7 mo; indurated wound after repeated surgery
12	[8]	(Child)				Giant-cell granulomas	Partial excision	Indurated wound
13	[8]	(Child)					Incision and drainage	Uncomplicated
14	[8]	(Child)	Traumatic lesion		Mild cough	Caseating granulomas	Incision and biopsy	Sinus for 4 mo; indurated scar
15	[2]	3 y/F	None	Cervical lymph node	Swelling lymphadenitis	Culture: positive for *M. malmoense*		Alive and well
16	[2]	5 y/F	None	Cervical lymph node	Swelling, lymphadenitis	Culture: positive for *M. malmoense*		Alive and well
17	[13]	9 mo	None	Cervical lymph node	Swelling	Direct smear: acid-fast bacilli; culture: positive for *M. malmoense*	Incision and drainage, antituberculous therapy (isoniazid, pyrazinamide, rifampin)	Sinus formation
							Second surgical intervention, continuous antituberculous two-drug regimen	Alive and well
18	[31]	3 y	None	Cervical lymph node	Cervical lymphadenitis	No acid-fast bacilli; culture: positive for *M. malmoense*		
19	[31]	8 y	None	Cervical lymph node	Cervical lymphadenitis	No acid-fast bacilli; culture: positive for *M. malmoense*		
20	[11]	75 y/F	None	Submandibular lymph node	Swelling	Culture: positive for *M. malmoense*		

Table 3. (*Continued*)

Case no.	Reference	Patient age (y)/sex	Underlying disease or risk factor	Site of infection	Clinical features	Diagnostic findings	Treatment	Outcome
21	[32]	2 y/F	None	Intrathoracic lymph nodes	History of wheezing and increasing exertional dyspnea unresponsive to salbutamol and oral coricosteroids, widespread rhonchi	Chest radiograph: superior mediastinal mass; computed tomography: paratracheal mass; histologic examination of lymph node: acid-fast bacilli, caseous necrosis; culture: positive for *M. malmoense*	Extrapleural approach (lymph nodes); no antituberculous therapy	Patient remained asymptomatic for the next 6 mo

NOTE. Blank spaces denote that data were not given.

M. malmoense have been reported [43]. In addition, the organism is not an obligate pathogen in the gastrointestinal tract. This is probably not the case for persons with severe immunodeficiency, however. For these patients the ATS has formulated separate criteria for the clinical significance of evidence of infection due to NTM [9]. The positivity of one smear prepared from feces or several stool cultures for a certain species of NTM is sufficient for the diagnosis of disseminated disease due to NTM in patients with immunodeficiency if other organ systems are involved and clinical signs of disease are present. Endoscopic biopsy of the gastrointestinal tract as a means of detecting mycobacteria and granulomas is rarely necessary and has only a limited diagnostic yield [49]. For HIV-seropositive patients with pulmonary infection due to *M. tuberculosis*, about 40% of the smears prepared from stool specimens are positive, but these patients do not have any clinical features of gastrointestinal *M. tuberculosis* infection [50–52]. Therefore, in this special situation the positive smears for acid-fast bacilli are not indicative of extrapulmonary infection due to *M. tuberculosis* (swallowed sputum containing mycobacteria) [53]. These findings do not pertain to gastrointestinal infections caused by NTM in HIV-infected patients. As we learned from experience with MAC infections, disseminated infection appears to be mostly of gastrointestinal origin. The presence of acid-fast bacilli in smears of stool specimens and/or the positivity of stool cultures for NTM are results of simple, noninvasive tests that correlate well with invasive disease if constitutional symptoms are present. Clinical signs of gastrointestinal disease in association with several positive smears and cultures and the exclusion of other pathogens are therefore sufficient evidence of invasive gastrointestinal disease due to NTM in patients with AIDS.

Susceptibility and Therapy

The results of susceptibility testing of *M. malmoense* are variable. This is probably due to the fact that the methodology is only standardized for tubercle bacilli and not for NTM. *M. malmoense* is normally susceptible to rifampin and resistant to isoniazid. Of the 21 cases of extrapulmonary infection due to *M. malmoense*, susceptibility results were available in only seven cases. Six strains were susceptible to ethambutol; five, to rifampin. Resistance to isoniazid was noted in all cases, and to each pyrazinamide and streptomycin, in two cases. In 1985 Banks et al. published a large review of treatment for patients with pulmonary disease due to *M. malmoense* [3]: he found poor correlation between results of in vitro susceptibility tests and clinical success. The best results with the lowest rate of relapses were achieved with the three-drug regimen of rifampin/ethambutol/isoniazid administered for 18–24 months. Omission of ethambutol was associated with an unfavorable course. Other regimens were also used with second-line drugs, including ethionamide and cycloserine, but the responses were poor. Four of ten nonresponders to antituberculous treatment underwent successful resectional surgery (most successful in cases of radiographically evident unilateral disease).

Lymphadenitis due to mycobacteria is a relatively common disease that was described in Shakespeare's *Macbeth* as scrofula or King's Evil. In contrast to incidence rates among adults, nontuberculous lymphadenitis due to NTM is more common than tuberculous lymphadenitis among children (except in developing countries); usually *M. avium* can be isolated [54–56]. The therapy of choice for nontuberculous lymphadenitis in general and for cervical lymphadenitis due to *M. malmoense* (the most frequent site of such infection) in

particular is total excision [55–59]. Treatment by means of incision with drainage, needle aspiration only, or partial excision should be avoided because of the high rate of associated complications such as sinus formation and scarring (see table 3). Medical treatment is usually not indicated.

Infection of a hand or forearm by NTM is uncommon [35]. In contrary to the treatment of infections of lymph nodes, the therapy necessary for local infections caused by traumatic injury in bursae is debridement and administration of a combination of antimycobacterial agents; otherwise, relapse is inevitable. In the case of isolation of *M. malmoense*, such a combination should include rifampin and ethambutol.

A review of cases of disseminated disease due to *M. malmoense* does not allow definite recommendations concerning the best therapeutic regimen. A combination including rifampin, isoniazid, and ethambutol was frequently used. In two cases of disseminated disease with leukemia as the underlying disease, the second-line drug cycloserine in combination with ethambutol was successful; the patients were cured. In our case there was a high resistance to both cycloserine and ethambutol, and we decided to treat with the alternative drugs rifabutin and clofazimine in combination with isoniazid. Omission of ethambutol did not impair the clinical success of treatment.

Conclusion

In general, extrapulmonary infection due to *M. malmoense* is a rare event. The most frequent infection site is the cervical lymph node. Disseminated infection has been reported to occur only in patients with severe immunodeficiency. The optimal therapy for infections due to *M. malmoense* is not well established. This is true not only for pulmonary manifestations but particularly for disseminated forms of infection because of their rare occurrence and association with different underlying diseases. The drugs associated with the most favorable susceptibility patterns are rifampin and ethambutol. An increasing number of *M. malmoense* isolates from sputum and from extrapulmonary sites of infection might be observed in the future in countries in which the prevalence of HIV and *M. malmoense* infections is high.

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